

**REMARKS**

Claims 1-5, 8-11, 14-17, 20-23, 26-29, 32-35, and 37-39 are presented for examination, claims 6, 7, 12, 13, 18, 19, 24, 25, 30, 31, and 36 having been withdrawn from consideration. Claims 1, 8, 14, 20, 26, and 32 are independent.

Applicants amend claims 1, 8, 14, 20, 26, and 32 herein to better claim the invention. No new matter is added. Support for the amendments may be found throughout the Specification and Figures as originally filed, and specifically in the Specification at page 41, second full paragraph. Applicants respectfully submit that the pending claims are in condition for allowance.

**Claim Objections**

In the Office Action, claims 8, 14, 26, and 32 were objected to because the Examiner considers the phrase “providing an indication .... if the amount the data gathered from the experiment differs from the generated dynamic behavior is greater than the predetermined amount” confusing. In order to expedite prosecution, Applicants amend claims 8, 14, 26, and 32 to recite providing an indication *if a difference between the data gathered from the experiment and the generated dynamic behavior is greater than the predetermined amount*. Applicants respectfully urge that this amendment addresses the Examiner’s concerns, and request that the claim objections be reconsidered and withdrawn.

**Claim Rejections under 35 U.S.C. §103(a)**

In the Office Action:

claims 1-5 and 20-23 were rejected under 35 U.S.C. §103(a) as being unpatentable over Sauro et al., Omics: A Journal of Integrative Biology, Vol. 7, No. 4, 2003 (hereafter “Sauro”) in view of Kurata et al., Nucleic Acids Research, Vol. 31, No. 14, p.4071-4084, 2003 (hereafter “Kurata”) in view of Funhashi et al., Biosilico, Vol. 1 No. 3, pp. 159-162, November 2003 (hereafter “Funhashi”) and further in view of U.S. Patent Publication No. 2002/0068269 to Allen (hereafter “Allen”) (See the Office Action, page 4);

claims 8-11, 14-17, 26-29, and 32-35 were rejected under 35 U.S.C. §103(a) as being unpatentable over Sauro, Kurata, and Funhashi, and further in view of U.S. Patent Publication No. 2003/0233218 to Schilling (hereafter “Schilling”);

claim 37 was rejected under 35 U.S.C. §103(a) as being unpatentable over Sauro, Kurata, Funhashi, and Allen, and further in view of Shannon et al., *Genome research*, Vol. 13, p. 2498-2504, 2003 (hereafter “Shannon”) and in view of *Presentation of Biospice*, DARPA BioComp, May 2002 (hereafter “Biospice”).

claims 38-39 were rejected under 35 U.S.C. §103(a) as being unpatentable over Sauro in view of Kurata Funhashi, Schilling, Shannon, and Biospice.

Applicants respectfully traverse the rejections.

Claims 1-5 and 20-23

Applicants’ claim 1 recites:

1. A system for improved modeling of a biological system that comprises a plurality of chemical reactions, the system comprising:

a modeling component comprising a graphical user interface for accepting user commands and input to construct or modify a model of the biological system;

a simulation engine accepting as input the constructed model of the biological system and generating as output dynamic behavior of the biological system; and

an analysis environment in communication with the simulation engine, the analysis environment

interfacing with data acquisition hardware that gathers data from an experiment, and

***using the output of the simulation engine to control a property of the experiment.***

In order to better claim the invention, Applicants amend claim 1 to include an analysis environment that interfaces with data acquisition hardware and ***uses the output of a simulation engine to control a property of an experiment.*** For example, the Specification at page 41 describes generating a model of an in situ experiment, the model being simulated by the simulation engine. The analysis environment, in conjunction with the data acquisition hardware, controls the experiment based on the results generated from the simulation engine. In one

example, the analysis environment may determine that the temperature of the experiment should be at 102 degrees Fahrenheit. If a thermocouple measuring a temperature of the in situ experiment registers a temperature below 102 degrees, the analysis environment may direct that more heat be applied to the experiment. Such a capability may be particularly useful, for example, in the construction of nanomachinery.

Applicants respectfully urge that Sauro, Kurata, and Funhashi, and Allen alone or in any reasonable combination, do not disclose or suggest at least an analysis environment that interfaces with data acquisition hardware and ***uses the output of a simulation engine to control a property of an experiment.***

Sauro describes a framework for integrating Systems Biology Workbench with BioSpice (Sauro at Abstract). At Figure 11, Sauro displays a screenshot of “JDesigner and Jarnac working together to carry out and display results of a simulation” (Sauro at page 366, caption of Figure 11, emphasis added). The underlying Jarnac software is a “script based simulation tool” (Sauro at page 364) that loads pregenerated SBML models. JDesigner is a “model design tool for editing biochemical networks visually” (Sauro at page 364). Nothing in the description of Jarnac or JDesigner mentions interfacing with ***using the output of the simulation engine to control a property of the experiment.***

Kurata describes using CADLIVE to construct a large-scale biochemical network based on a simulation-directed notation (Kurata at title and abstract, emphasis added). Like Sauro, Kurata addresses a generation and simulation of a biochemical network, and does not discuss ***using the output of the simulation engine to control a property of the experiment.***

Funhashi describes the CellDesigner software (Funhashi at page 159). CellDesigner may integrate with simulation models (Funhashi at page 160, first column), but CellDesigner is silent with respect to ***using the output of the simulation engine to control a property of the experiment.*** Indeed, CellDesigner describes the process of building a model at page 161, first and second columns; however, this passage does not ***using the output of the simulation engine to control a property of the experiment.***

The Examiner relies on Allen for an analysis environment that interfaces with data acquisition hardware (Office Action at page 6). Allen is generally directed to a method for examining pathways (Allen at Abstract). In Allen, a cellular biochemical pathway is simulated (Allen at paragraph [0011]). In some embodiments, data from a microarray is imported into the Simulation Module 10 (Allen at paragraph [0049]). Changes in the activity of diverse biological pathways is then evaluated or predicted; however, Allen does not use an analysis environment to control the experiment based on the results generated from a model. Accordingly, Allen is silent with respect to ***using the output of the simulation engine to control a property of the experiment.***

For at least the reasons set forth above, Applicants urge that Sauro, Kurata, Funhashi, and Allen alone or in any reasonable combination, do not disclose or suggest at least an ***analysis environment*** that ***interfaces with data acquisition hardware and uses the output of the simulation engine to control a property of the experiment,*** which is present in claim 1. Therefore, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claim 1 be withdrawn.

Claims 2-5 depend from independent claim 1 and, as such, incorporate all of the features of claim 1. Claims 2-5 are therefore allowable for at least the same reasons as claim 1. Applicants respectfully urge that dependent claims 2-5 recite additional patentable subject matter and respectfully request that the Examiner pass claims 2-5 to allowance.

Therefore, for at least the reasons set forth above, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claims 2-5 be withdrawn.

Independent claim 20 relates to a system that uses a simulation engine to generate an expected result of a chemical reaction as an output of the simulation engine. Claim 20 includes, among other things, ***using the output of the simulation engine to control a property of the experiment.*** As discussed above with respect to claim 1, Sauro, Kurata, Funhashi, and Allen alone or in any reasonable combination, do not disclose or suggest at least an ***analysis environment*** that ***uses the output of the simulation engine to control a property of the experiment.***

Claims 21-23 depend from claim 20, and therefore include each and every feature of claim 20. Accordingly, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claims 20-23 be withdrawn.

### Claims 8-11

Applicants' claim 8 recites:

8. A computer-implemented improved method for modeling a biological process comprising a plurality of chemical reactions, the method comprising:
  - providing a graphical user interface;
  - receiving, via the provided user interface, user commands and data;
  - constructing, using the received user commands and data, a model of the biological process;
  - generating, using the constructed model of the biological process, dynamic behavior of the modeled biological process; and
  - providing an indication that data gathered from an experiment and the generated dynamic behavior differ by an amount greater than a predetermined amount, if a difference between the data gathered from the experiment and the generated dynamic behavior is greater than the predetermined amount.*

Applicants respectfully urge that Sauro, Kurata, Funhashi, and Schilling, alone or in any reasonable combination, do not disclose or suggest at least: *providing an indication that data gathered from an experiment and the generated dynamic behavior differ by an amount greater than a predetermined amount, if a difference between the data gathered from the experiment and the generated dynamic behavior is greater than the predetermined amount*, which is present in claim 8.

As noted above neither Sauro nor Funhashi receive data gathered from an experiment. While the Examiner argues that Kurata receives data from an experiment, Kurata mentions receiving information from microarrays only in passing, and is silent with respect to *providing an indication that data gathered from an experiment and the generated dynamic behavior differ by an amount greater than a predetermined amount, if a difference between the data gathered from the experiment and the generated dynamic behavior is greater than the predetermined amount*. Accordingly, none of the Sauro, Funhashi, or Kurata references provide an indication when data gathered from an experiment differs from the generated dynamic

behavior of the modeled biological process. Instead, the Examiner relies on Schilling for this feature of claim 8.

Schilling is generally directed to a computer implemented process for constructing a scalable output network model of a bioparticle (Schilling at Abstract). The Examiner asserts, at page 11 of the Office Action, that Schilling discloses *providing an indication that data gathered from an experiment and the generated dynamic behavior differ by an amount greater than a predetermined amount, if a difference between the data gathered from the experiment and the generated dynamic behavior is greater than the predetermined amount* at paragraphs [0131] – [0135]. Applicants respectfully disagree.

In claim 8, data gathered from an experiment is compared to generated dynamic behavior of a system model. If the data differs from the generated dynamic behavior by more than a predetermined amount, an indication is provided. This is not what occurs in paragraphs [0131] – [0135] of Schilling.

At the cited passage, Schilling notes that certain reactions in a network may be more or less likely to occur. Less likely reactions may be removed from the model. However, a listing of evidence or reasons for why the reaction was removed should be provided (Schilling at paragraphs [0127]-[0128]). Therefore, Schilling allows a user to provide “confidence levels” that reflect a level of “confidence that the model developer has in the inclusion of the reaction in the model” (Schilling at paragraph [0129]). Schilling notes that the user’s level of confidence may be determined based on “published literature, documented experimental results, or results of computational analyses” (Schilling at paragraph [0129]). Different “data elements” are associated with network reaction components, and these data elements are ranked in terms of their importance toward determining the confidence level that will be assigned to the reaction (Schilling at paragraph [0131]).

Confidence levels are ranked in a hierarchy, and whether or not a reaction is included in a network model is determined based on the relative confidence levels in the hierarchy (Schilling at paragraph [0132]).

Accordingly, the cited passages of Schilling are directed to determining whether or not a given reaction will be included in a model. Nothing in these passages describe comparing model

results to data gathered from an experiment. Moreover, Schilling does not *provide an indication that data gathered from an experiment and the generated dynamic behavior differ by an amount greater than a predetermined amount.*

For at least the reasons set forth above, Applicants respectfully urge that Sauro, Kurata, Funhashi, and Schilling, alone or in any reasonable combination, do not disclose or suggest each and every feature of Applicants' claim 8. Therefore, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claim 8 be withdrawn.

Claims 9-11 depend from independent claim 8 and, as such, incorporate all of the features of claim 8. Therefore, for at least the reasons set forth above with respect to claim 8, Applicants respectfully urge that the above 35 U.S.C. §103(a) rejection of claims 9-11 be withdrawn.

#### Claims 14-17

Applicants' claim 14 is an "article of manufacture" claim corresponding to claim 8. Claim 14 includes: *computer-readable instructions for providing an indication that data gathered from an experiment and the generated dynamic behavior differ by an amount greater than a predetermined amount, if a difference between the data gathered from the experiment and the generated dynamic behavior is greater than the predetermined amount.*

Applicants respectfully urge that Sauro, Kurata, Funhashi, and Schilling, alone or in any reasonable combination, do not disclose or suggest each and every feature of Applicants' claim 14 for at least the same reasons as described above in relation to claim 8. Therefore, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claim 14 be withdrawn.

Claims 15-17 depend from independent claim 14 and, as such, incorporate all of the features of claim 14. The Examiner provides no justification for the rejection of claims 15-17, which recite additional patentable subject matter. Therefore, for at least the reasons set forth above with respect to claim 14, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claims 15-17 be withdrawn.

#### Claims 26-29

Applicants' claim 26 recites:

26. A computer-implemented method for integrated modeling, simulation and analysis of chemical reactions, the method comprising:  
providing a graphical user interface for accepting user commands and data;  
receiving, via the provided user interface, user commands and data;  
constructing, using the received user commands and data, a model of a chemical reaction;  
generating, using the constructed model of the chemical reaction, an expected result of the modeled chemical reaction; and  
*providing an indication that data gathered from an experiment and the generated expected result differ by an amount greater than a predetermined amount, if a difference between the data gathered from the experiment and the generated expected result is greater than the predetermined amount.*

Independent claim 26 generally corresponds to claim 8, except that claim 26 recites a "model of a chemical reaction" where claim 8 recites a "model of a biological system." Applicants respectfully urge that Sauro, Kurata, Funhashi, and Schilling, alone or in any reasonable combination, do not disclose or suggest at least *providing an indication that data gathered from an experiment and the generated expected result differ by an amount greater than a predetermined amount, if a difference between the data gathered from the experiment and the generated expected result is greater than the predetermined amount*, which is present in claim 26.

As discussed above with respect to claim 8, neither Sauro, Kurata, Funhashi nor Schilling compare *data gathered from an experiment* to *a generated expected result* from a simulation of a chemical reaction. Accordingly, these cited references do not *provide an indication* when the experimental result differs from the expected result. Therefore, for at least the reasons set forth above, Applicants respectfully urge that Sauro, Kurata, Funhashi, and Schilling, alone or in any reasonable combination, do not disclose or suggest each and every feature of Applicants' claim 26. Therefore, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claim 26 be withdrawn.

Claims 27-29 depend from independent claim 26 and, as such, incorporate all of the features of claim 26. Therefore, for at least the reasons set forth above with respect to claim 26.

Applicants respectfully request that the above 35 U.S.C. §102(a) rejection of claims 27-29 be Withdrawn.

Claims 32-35

Applicants' claim 32 is an "article of manufacture" claim corresponding to claim 26. Claim 32 includes: *computer-readable instructions for providing an indication that data gathered from an experiment and the generated expected result differ by an amount greater than a predetermined amount, if a difference between the data gathered from the experiment and the generated expected result is greater than the predetermined amount.*

For at least the reasons set forth above with respect to claim 26, Applicants respectfully urge that Sauro, Kurata, Funhashi, and Schilling, alone or in any reasonable combination, do not disclose or suggest each and every feature of Applicants' claim 32. Therefore, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claim 32 be withdrawn.

Claims 33-35 depend from independent claim 32 and, as such, incorporate all of the features of claim 32. Therefore, for at least the reasons set forth above with respect to claim 32, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claims 32-35 be withdrawn.

Claim 37

Claim 37 was rejected under 35 U.S.C. §103(a) as being unpatentable over Sauro in view of Kurata, Funhashi, Allen, Shannon, and BioSpice. Applicants respectfully traverse this rejection.

Claim 37 depends from claim 1, and therefore includes each feature of claim 1. As noted above with respect to claim 1, Sauro, Kurata, Funhashi, and Allen do not disclose or suggest at least *using the output of the simulation engine to control a property of the experiment*, which is present in claim 1. The addition of Shannon and BioSpice fails to cure the factual deficiencies of Sauro, Kurata, Funhashi, and Allen with respect to disclosing or suggesting this feature of claim 1.

Shannon describes Cytoscape, an application for “integrating biomolecular interaction networks with high-throughput expression data and other molecular states into a unified conceptual framework” (Shannon at Abstract). However, Shannon is entirely silent with respect to an ***analysis environment interfacing with data acquisition hardware, and using the output of the simulation engine to control a property of the experiment***, as included in claim 1.

Biospice is generally directed to an application to develop “a physically-grounded, molecular understanding of bacterial stress response,” “an infrastructure suitable for rapid deduction of pathway dynamics,” and “a theoretical and computational infrastructure [to] store, relate and model the data at different levels of abstraction” (Biospice at “Goals”). BioSpice is silent with respect to an ***analysis environment interfacing with data acquisition hardware, and using the output of the simulation engine to control a property of the experiment***, as included in claim 1.

For at least the reasons set forth above, Applicants respectfully urge that Sauro, Kurata, Funhashi, Allen, Shannon, and Biospice, alone or in any reasonable combination, do not disclose or suggest each and every feature of Applicants’ claim 37. Therefore, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claim 37 be withdrawn.

#### Claims 38-39

Claims 38-39 were rejected under 35 U.S.C. §103(a) as being unpatentable over Sauro in view of Kurata, Funhashi, Schilling, Shannon, and Biospice. Applicants respectfully traverse the rejection.

Claim 38 depends from claim 8, and therefore includes each and every feature of claim 8. Claim 39 depends from claim 14, and therefore includes each and every feature of claim 14. As noted above with respect to claims 8 and 14, Sauro, Kurata, Funhashi, and Schilling, alone or in any reasonable combination, do not disclose or suggest each and every feature of claims 8 and 14. The addition of Shannon and Biospice fails to cure the deficiencies of Sauro, Kurata, Funhashi, and Schilling with respect to disclosing or suggesting all of the features of claims 38 and 39.

Shannon describes Cytoscape, an application for “integrating biomolecular interaction networks with high-throughput expression data and other molecular states into a unified conceptual framework” (Shannon at Abstract). However, Shannon is entirely silent with respect to *providing an indication that data gathered from an experiment and the generated dynamic behavior differ by an amount greater than a predetermined amount, if the amount the data gathered from the experiment differs from the generated dynamic behavior is greater than the predetermined amount*, as included in claims 8 and 14.

Biospice is generally directed to an application to develop “a physically-grounded, molecular understanding of bacterial stress response,” “an infrastructure suitable for rapid deduction of pathway dynamics,” and “a theoretical and computational infrastructure [to] store, relate and model the data at different levels of abstraction” (Biospice at “Goals”). BioSpice is silent with respect to *providing an indication that data gathered from an experiment and the generated dynamic behavior differ by an amount greater than a predetermined amount, if the amount the data gathered from the experiment differs from the generated dynamic behavior is greater than the predetermined amount*, as included in claims 8 and 14.

For at least the reasons set forth above, Applicants respectfully urge that Sauro, Kurata, Funhashi, Schilling, Shannon, and Biospice, alone or in any reasonable combination, do not disclose or suggest each and every feature of Applicants’ claims 38-39. Therefore, Applicants respectfully request that the above 35 U.S.C. §103(a) rejection of claims 38-39 be withdrawn.

**CONCLUSION**

In light of the above, Applicants respectfully urge that all of the pending claims are in condition for allowance. Should the Examiner feel that a teleconference would expedite the prosecution of this application, the Examiner is urged to contact the Applicants' attorney at (617) 227-7400.

Please charge any shortage or credit any overpayment of fees to our Deposit Account No. 12-0080, under Order No. MWS-111RCE3. In the event that a petition for an extension of time is required to be submitted herewith, and the requisite petition does not accompany this response, the undersigned hereby petitions under 37 C.F.R. §1.136(a) for an extension of time for as many months as are required to render this submission timely. Any fee due is authorized to be charged to the aforementioned Deposit Account.

Dated: June 16, 2010

Respectfully submitted,

Electronic signature: /Kevin J. Canning/  
Kevin J. Canning  
Registration No.: 35,470  
LAHIVE & COCKFIELD, LLP  
One Post Office Square  
Boston, Massachusetts 02109-2127  
(617) 227-7400  
(617) 742-4214 (Fax)  
Attorney/Agent For Applicant